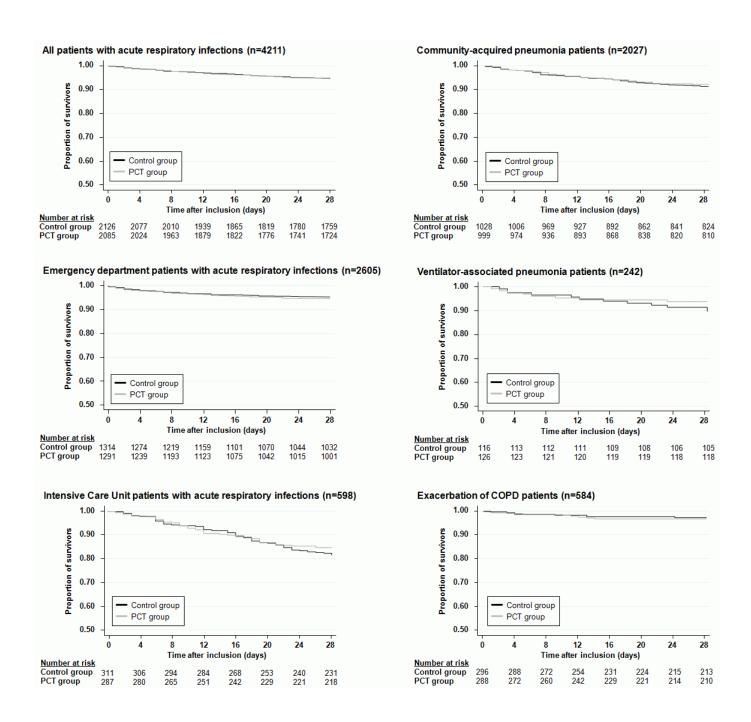
Extra web appendix 1. Definition of ARI subtype

ARI subtype	Definition
Upper respiratory infection	Clinical diagnosis of common cold, rhinosinusitis, pharyngitis, tonsillitis, otitis media or other unspecific upper respiratory infection; no additional diagnostic tests required. Definitions were similar among the two primary care trials.
Lower respiratory tract infection	Presence of at least one respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain) plus at least one finding during auscultation (rales, crepitation), or one sign of infection (core body temperature >38.0°C, shivering, leukocyte count >10`000cells/uL or <4`000cells/uL) independent of antibiotic pre-treatment
Acute bronchitis	Lower respiratory tract infection without infiltrate in the absence of an underlying lung disease or focal chest signs and infiltrates on chest X-ray
Community-acquired pneumonia (CAP)	Lower respiratory tract infection with a new infiltrate in the Chest X-ray admitted from the community. In the Kristoffersen trial, chest X-ray signs of pneumonia were not required for inclusion in the study.
Hospital-acquired pneumonia	Lower respiratory tract infection with a new infiltrate in the Chest X-ray in a patient in a hospital setting for at least 48–72hours
Ventilator-associated pneumonia (VAP)	ICU patients intubated for mechanical ventilation for >48 h with all of the following criteria: 1) clinically diagnosed with a new or persistent infiltrate on chest radiography associated with at least two of the following: purulent tracheal secretions, temperature >38C or, leukocyte count >11,000 mL or ,3,000 mL
Exacerbation of asthma	Episodic symptoms of airflow obstruction, which are at least partly reversible, as assessed by lung- function tests
Exacerbation of chronic obstructive pulmonary disease (ECOPD)	Sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD; defined by post-bronchodilator spirometric criteria according to the GOLD-guidelines; in patients with a clinical history of COPD and smoking, lung function testing at the time of inclusion was not mandatory

Legend: ARI, acute respiratory infection; COPD, chronic obstructive pulmonary disease;

Extra web appendix 2. Kaplan Maier curves for the risk of mortality within 30 days of follow up overall and in different subgroups



Legend: A. Overall; B. Emergency department; C. Intensive care unit; D. community-acquired pneumonia; E. Exaceration of COPD; F. ventilator associated pneumonia.

Extra web appendix 3. Sensitivity analyses

	PCT group	Control group	Adjusted OR (95%CI) ^a	p for interaction*
Main analysis (assumption	on that patients lost to follo	w-up did not experience a	n event)	
Mortality	118/2085 (5.7%)	134/2126 (6.3%)	0.94 (0.71, 1.23)	
Treatment failure	398/2085 (19.1%)	466/2126 (21.9%)	0.82 (0.71-0.97)	
Assumption that patients	s lost to follow-up experience	ced an event (death or tre	atment failure)	
Mortality	47/1188 (4%)	44/1195 (3.7%)	0.97 (0.6, 1.55)	
Treatment failure	410/2085 (19.7%)	476/2126 (22.4%)	0.84 (0.72, 0.98)	
Exclusion of patients lost	t to follow-up (complete case	e analysis)		
30 days mortality	118/2072 (5.7%)	134/2116 (6.3%)	0.94 (0.71, 1.23)	
Treatment failure	397/2072 (19.2%)	466/2116 (22%)	0.83 (0.71, 0.96)	
Excluding the ProRATA	A trial ¹			
Mortality	81/1902 (4.3%)	85/1915 (4.4%)	0.97 (0.61, 1.55)	0.81
Treatment failure	361/1902 (19%)	417/1915 (21.8%)	0.84 (0.71, 0.98)	0.94
Excluding all ICU trials				
Mortality	61/1798 (3.4%)	60/1815 (3.3%)	0.97 (0.61, 1.55)	0.55
Treatment failure	341/1798 (19%)	392/1815 (21.6%)	0.84 (0.72, 1.00)	0.88
Excluding all trials with	low adherence (<70%) or n	ot reporting adherence		
Mortality	61/1478 (4.1%)	65/1486 (4.4%)	0.97 (0.61, 1.55)	0.96
Treatment failure	313/1478 (21.2%)	366/1486 (24.6%)	0.82 (0.69, 0.98)	0.66
Excluding all trials without	out allocation concealment			
Mortality	78/1489 (5.2%)	92/1534 (6%)	0.93 (0.59, 1.49)	0.72
Treatment failure	312/1489 (21%)	357/1534 (23.3%)	0.85 (0.72, 1.02)	0.43
Excluding all trials withou	out blinded outcome assessn	nent		
Mortality	74/1463 (5.1%)	85/1506 (5.6%)	0.93 (0.59, 1.49)	0.87
Treatment failure	312/1463 (21.3%)	358/1506 (23.8%)	0.85 (0.71, 1.01)	0.47
Excluding all trials with	no follow up beyond hospita	al discharge		
Mortality	109/1954 (5.6%)	128/1996 (6.4%)	0.97 (0.6, 1.55)	0.25
Treatment failure	383/1954 (19.6%)	455/1996 (22.8%)	0.82 (0.71, 0.96)	0.26

Legend: *Analyses with individual patient data from all trials and added interaction terms (e.g. low adherence x PCT group) in the regression model to test for effect modifications. P-values <0.05 indicate evidence for effect modification. ¹Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375:(9713):463-74.

Extra web appendix 4. Further sensitivity analyses using meta-analysis with aggregated data (no covariable adjustment) to investigate heterogeneity

Overall Mortality by Clinical Setting, Mantel-Haenszel random effects

	PCT Algo	rithm	No PCT Algo	orithm		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	r M-H, Random, 95% CI
Primary care trials							
Briel 2008	0	232	1	226	0.7%	0.32 [0.01, 7.98] 200	8
Burkhardt 2010	0	275	0	275		Not estimable 201	
Subtotal (95% CI)		507		501	0.7%	0.32 [0.01, 7.98]	
Total events	0		1				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.69 (P	= 0.49)					
Emergency depart	ment trials	S					
Christ-Crain 2004	4	124	3	119	3.1%	1.29 [0.28, 5.88] 200	4
Christ-Crain 2006	18	151	20	151	15.6%	0.89 [0.45, 1.75] 200	
Stolz 2007	3	102	2	106	2.2%	1.58 [0.26, 9.63] 200	
Kristoffersen 2009	2	103	1	107	1.2%	2.10 [0.19, 23.51] 200	9 -
Schuetz 2009	34	671	33	688	30.1%	1.06 [0.65, 1.73] 200	
Long 2009	0	63	0	64		Not estimable 200	9
Long 2011	0	77	0	79		Not estimable 201	1
Subtotal (95% CI)		1291		1314	52.3%	1.05 [0.72, 1.52]	•
Total events	61		59				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.82, df	= 4 (P = 0.94)	$l^2 = 0\%$			
Test for overall effect: 2	Z = 0.26 (P	= 0.80)					
Intensive care unit	trials						
Nobre 2008	5	25	8	27	4.4%	0.59 [0.16, 2.14] 200	8
Schroeder 2009	0	4	0	4		Not estimable 200	9
Hochreiter 2009	7	24	5	19	4.0%	1.15 [0.30, 4.44] 200	9
Bouadma 2010	37	183	49	211	31.2%	0.84 [0.52, 1.36] 201	0
Stolz 2010	8	51	12	50	7.3%	0.59 [0.22, 1.59] 201	0
Subtotal (95% CI)		287		311	47.0%	0.79 [0.53, 1.17]	→
Total events	57		74				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.88, df	= 3 (P = 0.83)	$l^2 = 0\%$			
Test for overall effect: 2	Z = 1.18 (P	= 0.24)					
Total (95% CI)		2085		2126	100.0%	0.91 [0.70, 1.19]	*
Total events	118		134				
Heterogeneity: Tau ² =	0.00; Chi ² =	3.18, df	= 9 (P = 0.96)	; I ² = 0%			0.01 0.1 1 10 1
Test for overall effect: 2	Z = 0.68 (P	= 0.50)					0.01 0.1 1 10 1 Favours PCT Algorithm Favours No PCT Algor
Test for subgroup diffe	rences: Chi	$^{2} = 1.48$.	df = 2 (P = 0.4)	8). $I^2 = 0$	%		Tavours FCT Algorithm Favours NO PCT Algor

Overall Mortality by Clinical Setting, Peto fixed effects

	PCT Algo	rithm	No PCT Algo	orithm		Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year	Peto, Fixed, 95% CI
Primary care trials								
Briel 2008	0	232	1	226	0.5%	0.13 [0.00, 6.64]	2008	· ·
Burkhardt 2010	0	275	0	275		Not estimable	2010	
Subtotal (95% CI)		507		501	0.5%	0.13 [0.00, 6.64]		
Total events	0		1					
Heterogeneity: Not app	licable							
Test for overall effect: Z	Z = 1.01 (P =	0.31)						
Emergency departr	nent trials							
Christ-Crain 2004	4	124	3	119	3.2%	1.29 [0.29, 5.76]	2004	
Christ-Crain 2006	18	151	20	151	15.5%	0.89 [0.45, 1.75]	2006	
Stolz 2007	3	102	2	106	2.3%	1.56 [0.27, 9.19]	2007	
Kristoffersen 2009	2	103	1	107	1.4%	2.04 [0.21, 19.81]	2009	
Schuetz 2009	34	671	33	688	29.7%	1.06 [0.65, 1.73]	2009	-
Long 2009	0	63	0	64		Not estimable	2009	
Long 2011	0	77	0	79		Not estimable	2011	
Subtotal (95% CI)		1291		1314	52.1%	1.05 [0.73, 1.52]		•
Total events	61		59					
Heterogeneity: Chi ² = 0	.83, df = 4 (F	9 = 0.93;	$I^2 = 0\%$					
Test for overall effect: Z	Z = 0.27 (P =	0.79)						
Intensive care unit	trials							
Nobre 2008	5	25	8	27	4.6%	0.60 [0.17, 2.10]	2008	
Schroeder 2009	0	4	0	4		Not estimable	2009	
Hochreiter 2009	7	24	5	19	4.1%	1.15 [0.30, 4.33]	2009	
Bouadma 2010	37	183	49	211	31.2%	0.84 [0.52, 1.35]	2010	-
Stolz 2010 Subtotal (95% CI)	8	51 287	12	50 311	7.5% 47.5 %	0.60 [0.22, 1.58] 0.79 [0.54 , 1.17]	2010	•
Total events	57		74			- · · · · ·		
Heterogeneity: Chi ² = 0		9 = 0.83):						
Test for overall effect: Z	,	,,						
Total (95% CI)		2085		2126	100.0%	0.91 [0.70, 1.19]		*
Total events	118		134					
Heterogeneity: Chi ² = 3	.73, df = 9 (F	9 = 0.93);	$I^2 = 0\%$					
Test for overall effect: Z		, .						0.01 0.1 1 10 100 Favours PCT Algorithm Favours No PCT Algorithm
Test for subgroup differ	ences: Chi2:	= 2.03, df	= 2 (P = 0.36)	, I ² = 1.4%	, D			Tavours FOT Algorithm Favours No POT Algorithm

Overall Mortality by Adherence, Mantel-Haenszel random effects

	PCT Algo	rithm	No PCT Alg	orithm		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Adherence to PCT A	lgorithm >70	0%					
Briel 2008	0	232	1	226	0.7%	0.32 [0.01, 7.98]	-
Burkhardt 2010	0	275	0	275		Not estimable	
Christ-Crain 2004	4	124	3	119	3.1%	1.29 [0.28, 5.88]	
Christ-Crain 2006	18	151	20	151	15.6%	0.89 [0.45, 1.75]	- ■
Nobre 2008	5	25	8	27	4.4%	0.59 [0.16, 2.14]	
Schuetz 2009 Subtotal (95% CI)	34	671 1478	33	688 1486	30.1% 54.0%	1.06 [0.65, 1.73] 0.96 [0.66, 1.38]	•
Total events	61		65				
Heterogeneity: Tau ² =	0.00; Chi ² =	1.33, df	= 4 (P = 0.86);	$I^2 = 0\%$			
Test for overall effect:	Z = 0.24 (P =	= 0.81)					
Adherence to PCT Al	lgorithm <70	0% or no	t available				
Bouadma 2010	37	183	49	211	31.2%	0.84 [0.52, 1.36]	-
Hochreiter 2009	7	24	5	19	4.0%	1.15 [0.30, 4.44]	
Kristoffersen 2009	2	103	1	107	1.2%	2.10 [0.19, 23.51]	-
Long 2009	0	63	0	64		Not estimable	
Long 2011	0	77	0	79		Not estimable	
Schroeder 2009	0	4	0	4		Not estimable	
Stolz 2007	3	102	2	106	2.2%	1.58 [0.26, 9.63]	
Stolz 2010 Subtotal (95% CI)	8	51 607	12	50 640	7.3% 46.0%	0.59 [0.22, 1.59] 0.86 [0.58, 1.28]	•
Total events	57		69				
Heterogeneity: Tau ² =	0.00; Chi ² =	1.70, df	= 4 (P = 0.79);	$I^2 = 0\%$			
Test for overall effect:	Z = 0.74 (P =	= 0.46)					
Total (95% CI)		2085		2126	100.0%	0.91 [0.70, 1.19]	•
Total events	118		134				
Heterogeneity: Tau ² =	0.00; Chi ² =	3.18, df	= 9 (P = 0.96);	$I^2 = 0\%$			
Test for overall effect:	Z = 0.68 (P =	= 0.50)				Fa	0.01 0.1 1 10 100 avours experimental Favours control
Test for subgroup diffe	erences: Chi ²	t = 0.14	df = 1 (P = 0.7)	0), $I^2 = 0$	6		avours experimental if avours control

Treatment Failure by Clinical Setting, Mantel-Haenszel random effects

	PCT Algo	rithm	No PCT Alg	orithm		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Primary care trials							
Briel 2008	73	232	68	226	15.1%	1.07 [0.72, 1.59]	*
Burkhardt 2010 Subtotal (95% CI)	86	275 507	96	275 50 1	18.8% 33.9 %	0.85 [0.59, 1.21] 0.94 [0.72, 1.22]	•
Total events	159		164				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 0.71, d	f = 1 (P = 0.40)	0); $I^2 = 0$ %	6		
Test for overall effect:	Z = 0.46 (P	= 0.64)					
Emergency departme	ent trials						
Christ-Crain 2004	10	124	8	119	2.5%	1.22 [0.46, 3.20]	- -
Christ-Crain 2006	36	151	56	151	9.5%	0.53 [0.32, 0.87]	
Kristoffersen 2009	8	103	6	107	2.0%	1.42 [0.47, 4.24]	
Long 2009	4	63	6	64	1.4%	0.66 [0.18, 2.44]	
Long 2011	8	77	7	79	2.1%	1.19 [0.41, 3.47]	 - -
Schuetz 2009	103	671	130	688	29.5%	0.78 [0.59, 1.03]	-
Stolz 2007	13	102	15	106	3.7%	0.89 [0.40, 1.97]	
Subtotal (95% CI)		1291		1314	50.8%	0.78 [0.62, 0.96]	lack lack lack
Total events	182		228				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 5.01, d	f = 6 (P = 0.54)	4); $I^2 = 0\%$, 0		
Test for overall effect:	Z = 2.30 (P	= 0.02)					
Intensive care unit tr	ials						
Bouadma 2010	37	183	49	211	10.2%	0.84 [0.52, 1.36]	
Hochreiter 2009	7	24	5	19	1.3%	1.15 [0.30, 4.44]	
Nobre 2008	5	25	8	27	1.4%	0.59 [0.16, 2.14]	
Schroeder 2009	0	4	0	4		Not estimable	
Stolz 2010	8	51	12	50	2.4%	0.59 [0.22, 1.59]	
Subtotal (95% CI)		287		311	15.4%	0.79 [0.53, 1.17]	•
Total events	57		74				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 0.88, d	f = 3 (P = 0.83)	3); $I^2 = 0$ %	, 0		
Test for overall effect:	Z = 1.18 (P	= 0.24)					
Total (95% CI)		2085		2126	100.0%	0.83 [0.71, 0.97]	♦
Total events	398		466				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 7.88, d	f = 12 (P = 0.7	79); $I^2 = 0$	%	<u>├</u>	
Test for overall effect:			•				บา บ.า 1 10 100 ırs experimental Favours control
Test for subgroup diffe	rences: Ch	$i^2 = 1.28$	df = 2 (P = 0)	.53), I ² =	0%	ravoc	as experimental i avours control

Treatment Failure by Adherence, Mantel-Haenszel random effects

	PCT Algo	rithm	No PCT Alg	orithm		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Adherence to PCT Algorithm >70%									
Briel 2008	73	232	68	226	15.1%	1.07 [0.72, 1.59]			
Burkhardt 2010	86	275	96	275	18.8%	0.85 [0.59, 1.21]			
Christ-Crain 2004	10	124	8	119	2.5%	1.22 [0.46, 3.20]			
Christ-Crain 2006	36	151	56	151	9.5%	0.53 [0.32, 0.87]			
Nobre 2008	5	25	8	27	1.4%	0.59 [0.16, 2.14]			
Schuetz 2009 Subtotal (95% CI)	103	671 1478	130	688 1486	29.5% 76.9%	0.78 [0.59, 1.03] 0.81 [0.67, 0.99]	•		
Total events	313		366						
Heterogeneity: Tau ² =	0.01; Chi ² =	5.64, df	= 5 (P = 0.34)); I ² = 119	6				
Test for overall effect:	Z = 2.08 (P	= 0.04)							
Adherence to PCT Al	gorithm <7	0% or no	ot available						
Bouadma 2010	37	183	49	211	10.2%	0.84 [0.52, 1.36]			
Hochreiter 2009	7	24	5	19	1.3%	1.15 [0.30, 4.44]			
Kristoffersen 2009	8	103	6	107	2.0%	1.42 [0.47, 4.24]			
Long 2009	4	63	6	64	1.4%	0.66 [0.18, 2.44]			
Long 2011	8	77	7	79	2.1%	1.19 [0.41, 3.47]			
Schroeder 2009	0	4	0	4		Not estimable			
Stolz 2007	13	102	15	106	3.7%	0.89 [0.40, 1.97]			
Stolz 2010 Subtotal (95% CI)	8	51 607	12	50 640	2.4% 23.1 %	0.59 [0.22, 1.59] 0.88 [0.64, 1.22]	•		
Total events	85		100						
Heterogeneity: Tau ² =	0.00: Chi ² =	2.05. df	= 6 (P = 0.91)): I ² = 0%					
Test for overall effect:			,						
Total (95% CI)		2085		2126	100.0%	0.83 [0.71, 0.97]	•		
Total events	398		466						
Heterogeneity: Tau ² =	0.00; Chi ² =	7.88, df	= 12 (P = 0.7	9); I ² = 0%	6		0.01 0.1 1 10 100		
Test for overall effect:		0.01 0.1 1 10 100 vours experimental Favours control							
Test for subgroup diffe	rences: Chi	$^{2} = 0.18$	df = 1 (P = 0.0)	67), $I^2 = 0$	%	rav	ours experimental i avours control		